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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,870	10/27/2000	Redford B. Williams JR.	5405.239	5914

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/698,870	Williams
Examiner	**Art Unit**
Jehanne Souaya	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 4, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Currently, claims 1-16 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112

3. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 lacks sufficient antecedent basis for the phrase "said subject" as it is unclear whether this refers to the "human subject" previously recited in the claims. This rejection can be overcome by reciting instead --said human subject--.

Response to Arguments

4. The response asserts that the claims have been amended as suggested by the examiner. It is noted however, that claim 1 still recites "said subject" in line 3.

Enablement

5. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

Nature of the Invention

The claims are broadly drawn to screening human subjects for increased risk of disease in response to stimulus that induces a physiological stress response by determining the presence of

at least one serotonin transporter gene promoter long allele in a subject wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that the subject is at increased risk of any disease in response to stress. The claims are further drawn to embodiments wherein the disease is cardiovascular disease, cancer, autoimmune disease, delayed wound healing, and gastrointestinal disease. The claims are also broadly drawn to screening human subjects for increased risk of infectious disease wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that a subject is at increased risk of infectious disease, wherein the infectious disease can be as claimed in any of claims 7-15. Further, claim 1 does not recite any specific disease or type of stress, therefore the claim (and claims dependent therefrom with regard to the latter) broadly encompass any disease in response to any kind of stress. The specification further broadly defines "stress" as any physical or psychological stimulus that induces a physiological stress response (see p. 4, lines 29-32).

Presence and Absence of Working Examples

The specification has no working examples, whatsoever, of any studies or methods that associated the presence of any of the claimed diseases in human subjects with at least one long allele of the serotonin transporter gene promoter, either in combination or not with response to stress or any stimulus that induces a physiological stress response.

Amount of Direction and Guidance

The specification teaches analyzing human subjects, not including those with medical or psychiatric disorders or current medication use, for 5HIAA levels (primary serotonin metabolite)

in response to tryptophan depletion and response to the antagonist pindolol. The specification further analyzes differences in biological responses to tryptophan depletion or infusion, such as heart rate, mean arterial pressure, epinephrine and norepinephrine levels, cortisol levels, and prolactin levels in subjects with either short or long serotonin transporter gene promoter polymorphisms. The specification, however, does not provide any examples of an association between the presence of any of the claimed diseases and subjects with the long allele serotonin transporter gene polymorphism. Thus, while the study provided in the specification illustrates that subjects with different serotonin transporter gene promoter alleles have different biological responses to tryptophan infusion or depletion, the specification does not analyze the association between the presence of any of the claimed diseases and the long allele of the serotonin transporter gene promoter in subjects either in the presence or absence of a response to stress. It would essentially be a trial and error process to determine whether subjects with the long allele of the serotonin transporter gene promoter polymorphsims were in fact at an increased risk for developing any of either the broadly claimed category of diseases (ie: cardiovascular diseases, autoimmune diseases, infectious diseases, gastrointestinal diseases) or specific infectious diseases (ie: influenza, tuberculosis).

Level of predictability and unpredictability in the art

The art teaches that associations between the serotonin transport gene promoter alleles and different diseases is unpredictable. For example, Persico et al (American Journal of Medical Genetics, vol. 96, pp 123-127, 2000) teach that family based studies provide conflicting evidence

of linkage or association between either the short or the long allele of the serotonin transporter gene promoter in subjects with autistic disorder (see abstract) despite the fact that elevated serotonin blood levels have been consistently found in approximately 30-50% of autistic patients (see p. 123, col. 1, 2nd para). Further, Kunugi et al (American Journal of Medical Genetics, vol. 96, pp 307-309, 2000, abstract only) teach that while two independent research groups consistently reported a significant association between the serotonin transporter gene promoter short allele and late onset sporadic Alzheimer's disease, Kunugi et al could not find an association between such an allele and either early or late onset Alzheimer's disease in a Japanese population. Further, the post filing date art does not teach of any associations between any of the claimed diseases and either of the serotonin transporter gene promoter alleles, in combination or not with response to stress. Thus the art not only fails to support the efficacy of the invention, but in fact, supports the unpredictability of associating serotonin transport gene promoter alleles and different diseases, even diseases which were previously found to be associated with one of the alleles.

Quantity of Experimentation necessary

The quantity of experimentation in this area is extremely large since the claims are broadly drawn to broad categories of diseases and any type of stress and the specification does not support the scope of the broadly claimed invention. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d

1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. Furthermore, the Court in *Genetech Inc. V Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

To be able to practice the invention as broadly as it is claimed, that is to determine that a subject is at an increased risk for any disease in response to stress, or to a stimulus that induces a physiological stress response, at an increased risk for any of the claimed diseases in response to stress, or to a stimulus that induces a physiological stress response, or at an increased risk for any infectious disease or any of the claimed infectious diseases, merely based on the presence of at least one long allele of the serotonin transporter gene promoter, the skilled artisan would have to perform a large number of studies, that included a sufficient number of subjects suffering from different types of cardiovascular diseases, cancers, autoimmune diseases, gastrointestinal diseases, infectious diseases, as well as a sufficient number of control subjects, in the presence of and absence of different types of stress, to determine if in fact, a subject could be determined to be at an increased risk for developing any type of disease, or the diseases claimed, based on that subject having at least one long allele of the serotonin transporter gene promoter polymorphism.

Given the lack of guidance from the specification and the unpredictability taught in the art, such a study would be replete with trial and error analysis, the results of which are unpredictable. There is no teaching in either the specification or the art that the long allele of the serotonin transporter gene promoter is associated with *any* cardiovascular disease, such as hypertension, hypotension, or aneurysms, or gastrointestinal diseases, infectious diseases, delayed wound healing, cancers, or autoimmune diseases. These diseases each represent a large category of different disorders and diseases, wherein in many cases, each disease in the large category are involved with different biological mechanisms and genes and are associated with different risk factors and response to therapies. The specification merely provides an invitation for further experimentation and the claims are broadly drawn to methods that basically represent a research project, such research project requiring extensive trial and error analysis and which results are unknown and unpredictable, as illustrated by the state of the art at the time of filing.

Response to Arguments

6. The response traverses the rejection. The response asserts that the present inventor's finding on the relationship of the serotonin transporter long allele to stress as an indication of disease risk is accepted in the research community. The response cites Fumeron et al (Circulation, vol 105, pp 2943-2945, 2002) (which cites an article by the inventor) and Everson et al (Stroke, vol. 32, pp 1263-1270, 2001) as evidence of such. This argument as well as the cited references have been thoroughly reviewed but were found unpersuasive to overcome the

rejection. Firstly, it is noted that Fumeron et al do not teach any predictable correlation that a human subject is at an increased risk of any disease (including any cardiovascular disease, infectious disease, autoimmune disease, delayed would healing, and gastrointestinal disease, or cancer) in response to a stimulus that induces a physiological stress response, or stress in general, if the subject has at least one serotonin transporter gene promoter long allele. Fumeron et al teaches a study which found a significant correlation between MI (myocardial infarction) and the presence of two copies of the serotonin transporter long allele polymorphism (LL). It is noted however, that in comparing the LS (one copy long allele, one copy short allele) vs SS (two copies of the short allele) genotype, no significant correlation (P=0.38) was found (see table p. 2944). Thus Fumeron teaches that only the presence of two long alleles was associated with MI. Further, Fumeron teaches that there were no differences in alcohol consumption or smoking according to the polymorphism nor was there an interaction between these variables and the genotype on MI risk. Smoking is a stimulus that induces a physiological stress response. For example, Grassi et al, (Circulation, vol 90, pp 248-253, 1994) teach that cigarette spoking markedly and significantly increased mean arterial pressure, heart rate, calf vascular resistance, and plasma epinephrine and norepinephrine. Therefore, while Fumeron contemplate that the association between LL and MI risk *could* be due to the effect of the polymorphism on serotonin-mediated platelet activation or smooth muscle cell proliferation or other risk factors such as depression or response to stress, Fumeron does not teach that the association is actually due to such potential risk factor, and actually teaches the contrary with regard to stimuli that

induce a stress response such as smoking. It is noted that Fumeron does cite an article by the inventor, however this citation (see p. 2945, first para) is with regard to blood pressure and heart rate responses to mental stress protocols in persons with the L allele, but does not discuss the association of such with regard to any increased risk of disease or the broad categories of diseases claimed. Everson et al teach studying the impact of blood pressure reactivity and socioeconomic status on incident stroke, however the study by Everson et al did not assess the presence of the serotonin transporter promoter long allele in the subjects tested. Further, Everson et al do not teach any predictable correlation that a human subject is at an increased risk of any disease (including any cardiovascular disease, infectious disease, autoimmune disease, delayed would healing, and gastrointestinal disease, or cancer) in response to a stimulus that induces a stress response, or stress in general, if the subject has at least one serotonin transporter gene promoter long allele. Lastly, the response does not make clear how these publications indicate the ready applicability of the invention by skilled persons.

The response asserts that with regard to the Wands factors and nature of the invention, the invention is concerned with screening methods rather than therapeutic treatments. This argument has been thoroughly reviewed but was not found persuasive as the rejection set forth in the previous office action did not assert that the present invention was drawn to therapeutic treatments. Further, applicant is reminded that each case is examined on its own merits, with regard to the traversal that screening methods have received less scrutiny than therapeutic treatments for enablement historically.

With regard to the assertion that working examples are not considered a mandatory aspect of the disclosure, the previous response did not require a showing of working examples. It is noted, however, that because the specification lacks guidance and working examples to enable the full scope of the claimed invention, as set forth above, the teachings in the specification do not provide a predictable correlation that a human subject is at an increased risk of any disease (including any cardiovascular disease, infectious disease, autoimmune disease, delayed would healing, and gastrointestinal disease, or cancer) if the subject has at least one serotonin transporter gene promoter long allele, either in response or not, to stress in general or a stimulus that induces a stress response, to overcome the conflicting teachings taught in the art with regard to the unpredictability of an association between the presence of a serotonin transporter promoter long allele and any disease, such as Alzheimer's, or the lack of correlation between the presence of any stimulus which induces a physiological stress response, such as smoking, and the serotonin transporter promoter long allele in subjects with MI as taught by Fumeron.

The response further asserts that the stress response has been exhaustively studied and is well known, the long allele of the serotonin transporter is known, that determining whether a subject is both subjected to a stress response and carries the long allele can be carried with routine skill, and that the steps required by the claims and not the linkage recited by the claims should be the focus of the inquiry as the steps required by the claims can be carried out routinely. The response also submits that since the stress response is known and the long allele is known, little if any experimentation is required to implement the claims. This argument has been

thoroughly reviewed but was found unpersuasive because in the instant case, the lack of a teaching of linkage between the steps of the claims by the specification, and the conflicting teachings in the art of whether a linkage exists between the steps of the claims provide that the skilled artisan would essentially have to perform trial and error analysis to practice the broad scope of the claimed invention. As the results of such analysis are unpredictable as set forth in the previous office action and reiterated above, such trial and error analysis constitutes undue experimentation. Further, it is submitted that a large quantity of experimentation would have to be carried out by the skilled artisan as neither the specification nor the art teach a predictable correlation that a human subject is at an increased risk of any disease in general (including any cardiovascular disease in general, infectious disease, autoimmune disease, delayed would healing, and gastrointestinal disease, or cancer) in response to a stimulus that induces a stress response, or stress in general, if the subject has at least one serotonin transporter gene promoter long allele.

The response further asserts that the claims do not require the absolute prediction of disease but only "increased risk" of disease. This argument has been thoroughly reviewed but was found unpersuasive as the specification does not set forth or provide any predictable correlation that a subject is at "increased risk" of any disease in response stress or to a stimulus that induces a stress response if that subject has a serotonin transporter promoter long allele. The previous office action did not suggest or assert that an absolute prediction of disease was required. With regard to the traversal of the *Genentech* case cited in the previous office action,

the previous rejection's citation of *Genentech* was to illustrate that case law has established that the specification must supply the novel aspects of the invention in order to constitute adequate enablement. The novel aspects of the present invention involve a correlation between an increased risk of disease in response to stress or a stimulus that induces a stress response and the presence of a serotonin transporter promoter long allele. While the teachings of the instant specification illustrate that subjects with different serotonin transporter promoter alleles have different biological responses to tryptophan infusion or depletion, the specification does not analyze or provide any guidance as to the association between the presence of any of the claimed diseases in response to stress and the serotonin transporter promoter long allele. For these reasons and the reasons made of record in previous office action, this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

7. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Arinami et al., (Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999), [as defined by Grassi et al (Circulation, vol 90, pp 248-253, 1994)].

The claims are drawn to a method of screening human subjects for increased risk of disease, wherein the disease is cardiovascular disease (claim 2), in response to stimulus that induces a physiological stress response by determining the presence of at least one serotonin transporter long allele in a subject wherein the presence of at least one long allele serotonin

transporter gene promoter genotype indicates that said subject is at increased risk of disease in response to stress. Arinami teaches of analyzing patients with coronary artery disease for a serotonin transporter gene promoter polymorphism (see abstract, pp 853-854). Arinami teaches that the L allele (the long allele) was observed more frequently in patients with coronary heart disease ($p < 0.03$) and that this association was stronger ($p < 0.003$) in patients that also smoked. Although Arinami does not specifically state that smoking provides a stimulus that induces a physiological stress response, such a limitation is an inherent property of "smoking" [as evidenced by the disclosure of Grassi et al (abstract, col. 1, lines 18-22) which teaches that smoking markedly and significantly increased mean arterial pressure, heart rate, calf vascular resistance, and plasma norepinephrine and epinephrine levels]. Therefore, Arinami anticipates the claimed invention because Arinami teach a study which analyzed (screened) for an association between coronary heart disease (cardiovascular disease) and the long allele of the serotonin transport gene promoter in patients who smoked (stimulus that induces a physiological stress response).

Response to Arguments

8. The response traverses that the instant invention is concerned with "stimulus that induces a physiological stress response in a subject", and that smoking, as taught by Arinami fails to do this because smoking does not meet the definition of stress because to a smoker, it is the cessation of smoking, not the act of smoking itself, which is stressful. This argument has been

thoroughly reviewed but was found unpersuasive because smoking is inherently a stimulus that induces a physiological stress response in a subject. As evidenced by the teachings of Grassi et al (see abstract, col. 1, lines 18-22), smoking markedly and significantly increased mean arterial pressure, heart rate, calf vascular resistance, and plasma norepinephrine and epinephrine levels. It is further noted that the instant specification uses most of these criteria as examples in the definite of stress at p. 4, lines 30-32, (" *e.g.*, increased heart rate, increased blood pressure, and/or increased levels of hormones such as adrenalin..."). Therefore, the amendment to the claims, to include the limitation of "in response to a stimulus that induces a physiological stress response in the subject" is not sufficient to distinguish the claims from the teachings of Arinami. The rejection is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634

Jehanne Souaya
1/15/2003